Supporting Information

Synthesis of tetronic acids from propargylic alcohols and CO$_2$

Guo Shen,$^a$ Wen-Jun Zhou,$^{a,b,*}$ Xiao-Bo Zhang,$^a$ Guang-Mei Cao,$^a$ Zhen Zhang,$^{a,c}$ Jian-Heng Ye,$^a$
Li-Li Liao,$^a$ Jing Li,$^a$ and Da-Gang Yu$^{a,*}$

$^a$ Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, 29 Wangjiang Road, Chengdu 610064 (P. R. China) E-mail: dgyu@scu.edu.cn

$^b$ College of Chemistry and Chemical Engineering, Neijiang Normal University, Neijiang 641112 (P. R. China)

$^c$ College of Pharmacy and Biological Engineering, Chengdu University, Chengdu 610106 (P. R. China)
Content

1 General considerations ...........................................................................................................3
2 Synthesis of substrates ...........................................................................................................4
3 Synthesis of tetronic acid derivation ......................................................................................5
4 Crystal data for 2h (CCDC 1815711) .................................................................................6
5 Mechanistic studies ................................................................................................................7
  5.1 Carbonyl source confirmation .............................................................................................7
  5.1.1 The role of each reaction component .............................................................................7
  5.1.2 Carbon (13CO2) labeling experiment .............................................................................7
  5.2 The determination of the intermediate ..............................................................................8
  5.2.1 The role of the cyclic carbonate ....................................................................................8
  5.2.3 The role of the α-hydroxyl ketone .................................................................................8
  5.3 Demonstration of metal-free ...............................................................................................9
6 Gram-scale reaction ..................................................................................................................10
7 3-(2-bromophenyl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2S) ........................................10
8 CHARACTERIZATION DATA ................................................................................................11
9 References ..............................................................................................................................20
10 1H NMR, 19F NMR and 13C NMR spectra ............................................................................21
General considerations

All reactions were set up using 25 mL Schlenk techniques and carried out under a carbon dioxide atmosphere. All commercially available compounds were purchased from Accela, TCI, Adamas, Across, J&K or Micxy, and used as received unless otherwise noted. CO₂ (99.99% purity) was commercially available. Cesium carbonate (99%) was purchased from Accela. 1,3-Dimethyl-2-Imidazolidinone (DMI, >99.0% purity) was purchased from TCI and used directly without dehydration. The substrates of propargyl alcohol were synthesized according to the literature procedure. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.2±0.03 mm using UV light as a visualizing agent and iodine vapor to visualize the course of reaction.

A SHIMADZU-GL Wonda Cract ODS-2 column (5.0 μm, 4.6 x 150 mm) was used for the separation. The mobile phases were H₂O containing 1‰ HCOOH and MeOH. LC method A: A isocratic elution of 65:35 (v/v) MeOH/water over 11 min at a flow rate of 1.0 mL/min was used as a mobile phase. LC method B: A isocratic elution of 55:45 (v/v) MeOH/water for 4 min, then a linear gradient from 55:45 (v/v) MeOH/water (4 min) to 90% MeOH/water (6 min), next a isocratic elution 55:45 (v/v) MeOH/water from 6 min to 10 min, finally a linear gradient from 55:45 (v/v) MeOH/water (10 min) to 90% MeOH/water (11 min) and a isocratic elution 55:45 (v/v) MeOH/water from 11 min to 12 min at a flow rate of 1.0 mL/min was used as a mobile phase. UV detections were conducted at 254 nm. Metal element contents were obtained on a thermo ICP-AES (IRIS Adv.).

Flash column chromatography was performed over silica gel (200-300 mesh). Exact ESI mass spectra were performed on a SHIMADZU LCMS-IT-TOF. UPLC and UPLC-MS were obtained on a Waters UPLC and Thermo-ITQ.

¹H, ¹³C and ¹⁹F NMR spectra were recorded on a Bruker Advance 400 spectrometer (¹H: 400 MHz, ¹⁹F: 376 MHz, ¹³C: 101 MHz). Chemical shifts (δ) for ¹H, ¹⁹F and ¹³C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), dd (doublet of doublet). The residual solvent signals were used as references for ¹H and ¹³C NMR spectra and the chemical shifts converted to the TMS scale (DMSO-d₆: δH = 2.50 ppm, δC = 39.52 ppm).

GC-MS was obtained using electron ionization (Agilent Technologies 7890B/GC-System and 5977A/MSD). Exact ESI mass spectra were recorded on a SHIMADZU LCMS-IT-TOF. ESI-MS were obtained on a Thermo-ITQ. TLC was performed using commercially prepared 100-400 mesh silica gel plates (GF254), and visualization was effected at 254 nm.
**Synthesis of substrates**

The substrates 1b-1j and 1x were prepared according to procedures described in the literatures reported before.\[1\]

The substrates 1a, 1k-1w and 1y were prepared according to procedures described in the literatures reported before.\[2\]

The intermediate 3h was prepared according to procedures described in the literatures reported before.\[3\]

The compound 4h was prepared according to procedures described in the literatures reported before.\[4\]

All the protocols were employed without any optimization of the reaction conditions.
Synthesis of tetronic acid derivation

![Chemical Structure]

Propargyl alcohols 1 (0.4 mmol, 1.0 equiv.) were added into an oven-dried 25 mL Schlenk tube (synthware, F580825) equipped with a stirring bar, then added Cs$_2$CO$_3$ (1.6 mmol, 4.0 equiv.) in the glovebox. The tube was moved out and then evacuated and back-filled with CO$_2$ for 3 times. Once DMI (3 mL) was charged under CO$_2$ atmosphere, the Schlenk tube was sealed at atmospheric pressure of CO$_2$. The resulting solution was stirred at 65 °C. Then, the mixture was cooled to room temperature, quenched with 3 mL HCl solution (2 M) and the reaction mixture was extracted by EtOAc for 6-8 times. The combined organic layer was concentrated in vacuo. The residue was purified by flash silica gel chromatography (MeOH/DCM = 1:10) to give the tetronic acid products 2.
Crystal data for 2h (CCDC 1815711)

Datablock:

Bond precision: C-C = 0.0021 Å
Wavelength=0.71073 Å

Cell:
\[
a = 6.7868(6) \\
b = 8.5848(10) \\
c = 9.4383(8) \\
\alpha = 87.679(8) \\
\beta = 83.576(7) \\
\gamma = 73.938(9)
\]

Temperature: 291 K

<table>
<thead>
<tr>
<th>Calculated</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>525.10(9)</td>
</tr>
<tr>
<td>Space group</td>
<td>P -1</td>
</tr>
<tr>
<td>Hall group</td>
<td>-P 1</td>
</tr>
<tr>
<td>Moiety formula</td>
<td>C12 H12 O3</td>
</tr>
<tr>
<td>Sum formula</td>
<td>C12 H12 O3</td>
</tr>
<tr>
<td>Mr</td>
<td>204.22</td>
</tr>
<tr>
<td>Dx,g cm-3</td>
<td>1.292</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Mu (mm-1)</td>
<td>0.093</td>
</tr>
<tr>
<td>F000</td>
<td>216.0</td>
</tr>
<tr>
<td>F000'</td>
<td>216.12</td>
</tr>
<tr>
<td>h,k,lmax</td>
<td>8,10,11</td>
</tr>
<tr>
<td>Nref</td>
<td>2156</td>
</tr>
<tr>
<td>Tmin,Tmax</td>
<td>0.967,0.991</td>
</tr>
<tr>
<td>Tmin'</td>
<td>0.946</td>
</tr>
</tbody>
</table>

Correction method= # Reported T Limits: Tmin=0.739 Tmax=1.000
AbsCorr = MULTI-SCAN
Data completeness= 0.998
Theta(max)= 26.363
R(reflections)= 0.0479(1794)
wR2(reflections)= 0.1337(2152)
S = 1.053
Npar= 139
Mechanistic studies

Carbonyl source confirmation

The role of each reaction component

2-methyl-4-phenylbut-3-yn-2-ol 1h (0.4 mmol, 64.1 mg, 1.0 equiv.) were added into a 25 mL Schlenk tube equipped with a stirring bar, then added Cs₂CO₃ (1.6 mmol, 521.3 mg, 4.0 equiv., no Cs₂CO₃ in entry 3) in the glovebox. The tube was moved out and then evacuated and back-filled with CO₂ or N₂ for 3 times. Then the Schlenk tube was sealed at atmospheric pressure of CO₂ or N₂. The resulting solution was stirred for 48 h at 65 °C. Then, the mixture was cooled to room temperature, quenched with 3 mL HCl solution (2 M) and extracted with EA (6-8 times). The combined organic solution was concentrated at the reduced pressure. Column chromatography on silica gel (MeOH/DCM = 1:10) afforded the tetronic acid product 2h.

Carbon (¹³CO₂) labeling experiment

An oven-dried 25 mL Schlenk tube (synthware, F580825) equipped with a magnetic stir bar was charged with 2-methyl-4-phenylbut-3-yn-2-ol 1h (0.4 mmol, 64.1 mg, 1.0 equiv.) and Cs₂CO₃ (1.6 mmol, 521.3 mg, 4.0 equiv.) in the glovebox. The tube was moved out and then evacuated and back-filled with ¹³CO₂ for 3 times, DMI (3 mL) was injected in the Schlenk tube at room temperature under ¹³CO₂. The Schlenk tube was sealed at atmospheric pressure of ¹³CO₂ (1 atm). The resulting mixture was stirred at 65 °C for 48 h. Then, the mixture was cooled to room temperature, quenched with 3 mL HCl solution (2 M) and extracted with EA (6-8 times). The combined organic solution was concentrated at the reduced pressure. Column chromatography on silica gel afforded tetronic acid 2h’ in 72% yield. The ¹³C-content was determined to be 92% by HRMS (ESI+).

¹H NMR (400 MHz, DMSO-d₆) δ 7.94 – 7.87 (m, 2H), 7.36 (t, J = 7.7 Hz, 2H), 7.25 – 7.18 (m, 1H), 1.51 (s, 6H); ¹³C NMR (101 MHz, DMSO-d₆) δ 181.08 (d, J = 11.4 Hz),
171.42, 131.37 (d, J = 3.9 Hz), 128.40, 127.03 (d, J = 2.2 Hz), 126.59, 96.31 (d, J = 71.5 Hz), 80.03, 24.54. HRMS (ESI+): calculated for C_{11}H_{13}O_3 [M+H]^+ 206.0893, found 206.0894.

The determination of the intermediate

The role of the cyclic carbonate

An oven-dried 25 mL Schlenk tube (synthware, F580825) equipped with a magnetic stir bar was charged with cyclic carbonate 3h (0.4 mmol, 81.7 mg, 1.0 equiv.) and Cs_2CO_3 (1.6 mmol, 521.3 mg, 4.0 equiv.) in the glovebox. The tube was moved out and then evacuated and back-filled with CO_2 or N_2 for 3 times, DMI (3 mL) was injected in the Schlenk tube at room temperature under CO_2 or N_2. The Schlenk tube was sealed at atmospheric pressure of CO_2 or N_2 (1 atm). The resulting mixture was stirred at 65 °C for 48 h. Then, the mixture was cooled to room temperature, quenched with 3 mL HCl solution (2 M) and extracted with EA (6-8 times). The combined organic solution was concentrated at the reduced pressure. Column chromatography on silica gel afforded product 2h. These yields evidences proved alkylidene cyclic carbonates was the key intermediate, and control experiments revealed that Cs_2CO_3 was necessary in the conversion to products. The higher yield under N_2 than CO_2 atmosphere might indicate that basic property could affect the ring-opening process and CO_2 could decrease the alkaline of the system.

The role of the α-hydroxyl ketone

An oven-dried 25 mL Schlenk tube (synthware, F580825) equipped with a magnetic
stir bar was charged with α-hydroxyl ketone 4h (0.4 mmol 71.3 mg, 1.0 equiv.) and Cs$_2$CO$_3$ (1.6 mmol, 521.3 mg, 4.0 equiv.) in the glovebox. The tube was moved out and then evacuated and back-filled with CO$_2$ for 3 times, DMI (3 mL) was injected in the Schlenk tube at room temperature under CO$_2$. Then the Schlenk tube was sealed at atmospheric pressure of CO$_2$ (1 atm). The resulting mixture was stirred at 65 °C for 11 h. Then, the mixture was cooled to room temperature, quenched with 3 mL HCl solution (2 M), and 2h wasn't detected by ESI-MS.

**Demonstration of metal-free**

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Co/ppm</th>
<th>Cu/ppm</th>
<th>Fe/ppm</th>
<th>Ni/ppm</th>
<th>Ag/ppm</th>
<th>Rh/ppm</th>
<th>Pd/ppm</th>
<th>Mn/ppm</th>
<th>Ru/ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0118</td>
<td>0.0165</td>
<td>0.5186</td>
<td>0.0155</td>
<td>0.0096</td>
<td>0.0438</td>
<td>0.0151</td>
<td>0.0199</td>
<td>0.0051</td>
</tr>
</tbody>
</table>

An oven-dried 25 mL Schlenk tube (synthware, F580825) equipped with a magnetic stir bar was charged with substance 1h (0.4 mmol, 64.1 mg, 1.0 equiv.) and Cs$_2$CO$_3$ (1.6 mmol, 521.3 mg, 4.0 equiv.) in the glovebox. The tube was moved out and then evacuated and back-filled with carbon dioxide for 3 times, DMI (3 mL) was injected in the Schlenk tube at room temperature under CO$_2$. The Schlenk tube was sealed at atmospheric pressure of CO$_2$ (1 atm). The resulting mixture was stirred at 65 °C for 48 h. Then, the mixture was cooled to room temperature. The reaction mixture was concentrated at the reduced pressure. The residue was diluted to 30.7 mg/mL, and mixed again for ICP experiment.
An oven-dried 250 mL Schlenk flask equipped with a magnetic stir bar was charged with substance 1s (8.0 mmol, 1.9129 g, 1.0 equiv.) and Cs$_2$CO$_3$ (32 mmol, 10.4769 g, 4.0 equiv.) in the glovebox. The tube was moved out and then evacuated and back-filled with carbon dioxide for 3 times, DMI (60 mL) was injected in the Schlenk flask at room temperature under CO$_2$. The resulting mixture in sealed tube was stirred at 65 °C for 48 h (Re-fill with CO$_2$ was performed at 36 h.). Then, the mixture was cooled to room temperature, quenched with HCl solution (2 M) and extracted with EA (6-8 times). The combined organic solution was concentrated at the reduced pressure. Twice column chromatography on silica gel afforded product 2s in 79% yield since we didn't get the pure product for the first purification.
Characterization data

4-(4-hydroxy-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-yl)benzonitrile (2a)

82.3 mg, 0.359 mmol, 90%; White powder; Rf (MeOH/DCM 1/10): 0.12;

$^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.36 (d, $J$ = 8.7 Hz, 2H), 7.62 (d, $J$ = 8.7 Hz, 2H), 1.35 (s, 6H); $^{13}C$ NMR (101 MHz, DMSO-$d_6$) $\delta$ 193.12, 173.91, 141.68, 131.73, 123.62, 120.73, 103.50, 87.27, 80.51, 25.01.

HRMS (ESI-MS, m/z): calculated m/z for [C$_{13}$H$_{11}$NO$_3$] [M-H]: 228.0666, found: 228.0669.

4-(4-hydroxy-5-methyl-2-oxo-5-phenyl-2,5-dihydrofuran-3-yl)benzonitrile (2b)

78.4 mg, 0.322 mmol, 81%; White powder; Rf (MeOH/DCM 1/10): 0.12;

$^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.47 (d, $J$ = 8.4 Hz, 2H), 7.48 (d, $J$ = 8.6 Hz, 2H), 1.67 – 1.46 (m, 2H), 1.19 (s, 3H), 0.71 (t, $J$ = 7.4 Hz, 3H); $^{13}C$ NMR (101 MHz, DMSO-$d_6$) $\delta$ 187.53, 172.87, 139.02, 132.07, 125.28, 120.17, 105.93, 92.61, 83.07, 29.64, 23.52, 7.89.

HRMS (ESI-MS, m/z): calculated m/z for [C$_{14}$H$_{13}$NO$_3$] [M-H]: 304.0979, found: 304.0973.

4-(5,5-diethyl-4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)benzonitrile (2c)

64.1 mg, 0.249 mmol, 62%; White powder; Rf (MeOH/DCM 1/10): 0.11;

$^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.18 (d, $J$ = 8.2 Hz, 2H), 7.79 (d, $J$ = 8.2 Hz, 2H), 1.94 – 1.78 (m, 4H), 0.73 (t, $J$ = 7.3 Hz, 6H); $^{13}C$ NMR (101 MHz, DMSO-$d_6$) $\delta$ 181.36, 171.86, 136.65, 132.42, 126.69, 119.72, 108.09, 97.63, 85.87, 28.49, 7.50.

HRMS (ESI-MS, m/z): calculated m/z for [C$_{15}$H$_{15}$NO$_3$] [M-H]: 282.1136, found:
282.1129.

4-(4-hydroxy-5-methyl-2-oxo-5-phenyl-2,5-dihydrofuran-3-yl)benzonitrile (2d)

![Structure Image]

102.8 mg, 0.353 mmol, 88%, (2 equiv. Cs$_2$CO$_3$, 48 h); 101.9 mg, 0.350 mmol, 87%, (4 equiv. Cs$_2$CO$_3$, 2 h); White powder; $R_f$ (MeOH/DCM 1/10): 0.07;

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.43 (d, $J = 8.3$ Hz, 2H), 7.49 (dd, $J = 16.4, 8.0$ Hz, 4H), 7.36 – 7.26 (m, 2H), 7.26 – 7.19 (m, 1H), 1.60 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 192.09, 174.60, 142.59, 128.31, 127.38, 125.49, 123.18, 120.84, 103.00, 85.82, 82.82, 25.05.

HRMS (ESI-MS, m/z): calculated m/z for [C$_{18}$H$_{13}$NO$_3$] [M-H]: 290.0823, found: 290.0812.

4-(4-hydroxy-2-oxo-1-oxaspiro[4.6]undec-3-en-3-yl)benzonitrile (2e)

![Structure Image]

86.6 mg, 0.339 mmol, 85%; White powder; $R_f$ (MeOH/DCM 1/10): 0.10;

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.21 (d, $J = 8.6$ Hz, 2H), 7.77 (d, $J = 8.6$ Hz, 2H), 2.22 – 2.08 (m, 2H), 1.89 – 1.78 (m, 4H), 1.78 – 1.68 (m, 2H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 182.37, 171.32, 137.22, 132.33, 126.39, 119.79, 107.68, 95.38, 90.49, 36.55, 25.15.

HRMS (ESI-MS, m/z): calculated m/z for [C$_{15}$H$_{13}$NO$_3$] [M-H]: 254.0823, found: 254.0823.

4-(4-hydroxy-2-oxo-1-oxaspiro[4.5]dec-3-en-3-yl)benzonitrile (2f)

![Structure Image]

96.6 mg, 0.359 mmol, 90%, (2 equiv. Cs$_2$CO$_3$, 48 h); 100.5 mg, 0.373 mmol, 93%, (4 equiv. Cs$_2$CO$_3$, 2 h); White powder; $R_f$ (MeOH/DCM 1/10): 0.10;

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.21 (d, $J = 8.6$ Hz, 2H), 7.77 (d, $J = 8.6$ Hz, 2H), 1.99 – 1.91 (m, 2H), 1.73 – 1.70 (m, 3H), 1.61 – 1.48 (m, 4H), 1.28 – 1.18 (m, 1H); $^{13}$C NMR
(101 MHz, DMSO-$d_6$) δ 185.51, 171.63, 137.68, 132.25, 126.35, 119.86, 107.38, 93.77, 81.82, 32.50, 24.48, 22.07.

**HRMS (ESI-MS, m/z):** calculated m/z for [C$_{16}$H$_{15}$NO$_3$][M-H]: 268.0979, found: 268.0972.

**4-(4-hydroxy-2-oxo-1-oxaspiro[4.6]undec-3-en-3-yl)benzonitrile (2g)**

![Chemical Structure](image)

93.6 mg, 0.330 mmol, 83%; White powder; $R_f$ (MeOH/DCM 1/10): 0.09;

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.14 (d, $J = 8.6$ Hz, 2H), 7.78 (d, $J = 8.6$ Hz, 2H), 2.15 – 2.01 (m, 2H), 1.80 – 1.61 (m, 8H), 1.61 – 1.48 (m, 2H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 190.76, 173.10, 139.91, 131.93, 124.92, 120.36, 105.16, 89.69, 84.65, 36.63, 28.33, 22.61.

**HRMS (ESI-MS, m/z):** calculated m/z for [C$_{17}$H$_{17}$NO$_3$][M-H]: 282.1136, found: 282.1129.

**4-hydroxy-5,5-dimethyl-3-phenylfuran-2(5H)-one (2h)**

![Chemical Structure](image)

59.6 mg, 0.292 mmol, 73%; White powder; $R_f$ (MeOH/DCM 1/10): 0.38;

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.91 – 7.86 (m, 2H), 7.37 (t, $J = 7.8$ Hz, 2H), 7.26 – 7.20 (m, 1H), 1.52 (s, 6H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 181.06, 171.41, 131.36, 128.40, 127.03, 126.60, 96.33, 80.03, 24.54.

**HRMS (ESI-MS, m/z):** calculated m/z for [C$_{12}$H$_{12}$O$_3$][M+H]$^+$: 205.0859, found: 205.0857.

**3-(4-fluorophenyl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2i)**

![Chemical Structure](image)

63.0 mg, 0.284 mmol, 71%; White powder; $R_f$ (MeOH/DCM 1/10): 0.25;

$^1$H NMR (400 MHz, DMSO-$d_6$) (400 MHz, DMSO-$d_6$) δ 8.03 – 7.97 (m, 2H), 7.18 (t, $J = 9.0$ Hz, 2H), 1.43 (s, 6H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 182.24, 171.79, 160.56 (d, $J$
$\delta$ 242.9 Hz), 128.46 ($d, J = 7.5$ Hz), 128.39, 115.11 ($d, J = 20.9$ Hz), 94.47, 80.18, 24.57; $^{19}$F NMR (376 MHz, DMSO-$d_6$) $\delta$ -115.08.

HRMS (ESI-MS, m/z): calculated $m/z$ for $[C_{12}H_{11}FO_3]$ [M-H]$: 221.0619, found: 221.0618.

3-(4-chlorophenyl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2j)

\[ \text{Cl} \]

75.3 mg, 0.316 mmol, 79%; White powder; $R_f$ (MeOH/DCM 1/10): 0.20;

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.01 ($d, J = 8.8$ Hz, 2H), 7.40 ($d, J = 8.7$ Hz, 2H), 1.49 ($s$, 6H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 183.10, 171.63, 131.01, 130.26, 128.32, 128.08, 94.15, 80.25, 24.55.

HRMS (ESI-MS, m/z): calculated $m/z$ for $[C_{12}H_{11}ClO_3]$ [M-H]$: 239.0469, found: 239.0469.

3-(4-bromophenyl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2k)

\[ \text{Br} \]

97.3 mg, 0.344 mmol, 86%; White powder; $R_f$ (MeOH/DCM 1/10): 0.15;

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.89 ($d, J = 8.7$ Hz, 2H), 7.56 ($d, J = 8.6$ Hz, 2H), 1.50 ($s$, 6H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 181.51, 171.09, 131.39, 130.63, 128.82, 119.44, 95.42, 80.25, 24.44.

HRMS (ESI-MS, m/z): calculated $m/z$ for $[C_{12}H_{11}BrO_3]$ [M-H]$: 280.9819, found: 280.9835.

3-([1,1'-biphenyl]-4-yl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2l)

90.5 mg, 0.323 mmol, 81%; White powder; $R_f$ (MeOH/DCM 1/10): 0.3;

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.03 – 7.97 (m, 2H), 7.72 – 7.67 (m, 4H), 7.47 (dd, $J = 8.4$, 6.9 Hz, 2H), 7.39 – 7.33 (m, 1H), 1.54 ($s$, 6H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$
180.69, 171.25, 140.29, 138.28, 130.38, 129.39, 127.79, 127.58, 126.90, 126.64, 96.47, 80.13, 24.53.

**HRMS** (ESI-MS, m/z): calculated m/z for \([\text{C}_{18}\text{H}_{16}\text{O}_3]\) [M-H]: 279.1027, found: 279.1030.

4-hydroxy-5,5-dimethyl-3-(\(\rho\)-tolyl)furan-2(5\(H\))-one (2m)

\[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{O} \\
\text{H}
\end{array}
\]

50.5 mg, 0.231 mmol, 58%; White powder; \(R_f\) (MeOH/DCM 1/10): 0.4;

**\(^1\)H NMR** (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.79 (d, \(J = 8.3\) Hz, 2H), 7.17 (d, \(J = 8.0\) Hz, 2H), 2.29 (s, 3H), 1.50 (s, 6H); **\(^{13}\)C NMR** (101 MHz, DMSO-\(d_6\)) \(\delta\) 180.16, 171.42, 135.77, 128.98, 128.31, 127.01, 96.58, 79.96, 24.55, 21.31.

**HRMS** (ESI-MS, m/z): calculated m/z for \([\text{C}_{13}\text{H}_{14}\text{O}_3]\) [M+H]\(^+\): 219.1016, found: 219.1016.

ethyl 4-(4-hydroxy-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-yl)benzoate (2n)

\[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{O} \\
\text{H}
\end{array}
\]

85.4 mg, 0.309 mmol, 77% (2 equiv. Cs\(_2\)CO\(_3\), 48 h); 83.8 mg, 0.303 mmol, 76% (4 equiv. Cs\(_2\)CO\(_3\), 2 h); White powder; \(R_f\) ((MeOH/DCM): 0.20;

**\(^1\)H NMR** (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.23 (d, \(J = 8.6\) Hz, 2H), 7.87 (d, \(J = 8.0\) Hz, 2H), 4.29 (q, \(J = 7.1\) Hz, 2H), 1.41 (s, 6H), 1.32 (t, \(J = 7.1\) Hz, 3H); **\(^{13}\)C NMR** (101 MHz, DMSO-\(d_6\)) \(\delta\) 187.78, 172.52, 166.26, 138.98, 129.16, 125.49, 125.00, 91.81, 80.34, 60.72, 24.73, 14.70.

**HRMS** (ESI-MS, m/z): calculated m/z for \([\text{C}_{15}\text{H}_{16}\text{O}_5]\) [M-H]: 275.0925, found: 275.0922.

4-hydroxy-5,5-dimethyl-3-(4-nitrophenyl)furan-2(5\(H\))-one (2o)

\[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{O} \\
\text{H}
\end{array}
\]

85.5 mg, 0.309 mmol, 77% (2 equiv. Cs\(_2\)CO\(_3\), 48 h); 83.8 mg, 0.303 mmol, 76% (4 equiv. Cs\(_2\)CO\(_3\), 2 h); White powder; \(R_f\) ((MeOH/DCM): 0.20;
72.2 mg, 0.290 mmol, 72%; Yellow powder; Rf (MeOH/DCM 1/10): 0.13;

\(^1\text{H NMR}\) (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.37 – 8.30 (m, 2H), 8.22 – 8.14 (m, 2H), 1.47 (s, 6H);

\(^{13}\text{C NMR}\) (101 MHz, DMSO-\(d_6\)) \(\delta\) 187.45, 171.69, 143.95, 140.73, 125.65, 123.83, 92.54, 80.61, 24.56.

HRMS (ESI-MS, m/z): calculated m/z for \([C_{12}H_{11}NO_5]\) [M+H]: 248.0564, found: 248.0564.

4-hydroxy-5,5-dimethyl-3-(4-(trifluoromethyl)phenyl)furan-2(5H)-one (2p)

83.8 mg, 0.308 mmol, 77% (2 equiv. Cs\(_2\)CO\(_3\), 48 h); 86.2 mg, 0.317 mmol, 79% (4 equiv. Cs\(_2\)CO\(_3\), 2 h); Yellow powder; Rf (MeOH/DCM 1/10): 0.18;

\(^1\text{H NMR}\) (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.17 (d, \(J = 8.2\) Hz, 2H), 7.72 (d, \(J = 8.2\) Hz, 2H), 1.53 (s, 6H);

\(^{13}\text{C NMR}\) (101 MHz, DMSO) \(\delta\) 182.92, 170.97, 135.72, 127.08, 126.60 (q, \(J = 31.7\) Hz), 125.26 (q, \(J = 3.8, 3.3\) Hz), 124.84 (q, \(J = 271.8\) Hz), 95.19, 80.36, 24.41; \(^{19}\text{F NMR}\) (376 MHz, DMSO-\(d_6\)) \(\delta\) -61.46.

HRMS (ESI-MS, m/z): calculated m/z for \([C_{13}H_{11}F_3O_3]\) [M-H]: 271.0588, found: 271.0596.

3-(4-benzoylphenyl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2q)

103.5 mg, 0.328 mmol, 84%; White powder; Rf (MeOH/DCM 1/10): 0.25;

\(^1\text{H NMR}\) (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.03 – 8.00 (m, 2H), 7.69 (dd, \(J = 8.3, 1.9\) Hz, 4H), 7.47 (t, \(J = 7.7\) Hz, 2H), 7.38 – 7.34 (m, 1H), 1.54 (s, 6H); \(^{13}\text{C NMR}\) (101 MHz, DMSO-\(d_6\)) \(\delta\) 195.71, 182.65, 170.91, 137.78, 135.93, 134.70, 132.95, 130.12, 129.99, 129.00, 126.59, 95.83, 80.32, 24.44.

HRMS (ESI-MS, m/z): calculated m/z for \([C_{13}H_{16}O_4]\) [M-H]: 307.0976, found: 307.0965.

4-hydroxy-5,5-dimethyl-3-(4-(trifluoromethoxy)phenyl)furan-2(5H)-one (2r)
89.8 mg, 0.312 mmol, 78%; White powder; \( R_f \) (MeOH/DCM 1/10): 0.28;

\(^1\)H NMR (400 MHz, DMSO-\( d_6 \)) \( \delta \) 8.03 (d, \( J = 9.0 \) Hz, 2H), 7.37 (d, \( J = 7.9 \) Hz, 2H), 1.52 (s, 6H); \(^{13}\)C NMR (101 MHz, DMSO-\( d_6 \)) \( \delta \) 186.03, 175.80, 151.56 (d, \( J = 2.1 \) Hz), 135.37, 133.44, 125.86, 125.33 (q, \( J = 255.9 \) Hz), 100.32, 85.02, 29.15; \(^{19}\)F NMR (376 MHz, DMSO-\( d_6 \)) \( \delta \) -56.86.

HRMS (ESI-MS, m/z): calculated m/z for \([C_{13}H_{11}F_3O_4][-H]^+\): 287.0537, found: 287.0539.

3-(2-bromophenyl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2s)

95.5 mg, 0.337 mmol, 84%; White powder; \( R_f \) (MeOH/DCM 1/10): 0.30;

\(^1\)H NMR (400 MHz, DMSO-\( d_6 \)) \( \delta \) 7.69 – 7.64 (m, 1H), 7.42 – 7.37 (m, 1H), 7.31 – 7.25 (m, 2H), 1.49 (s, 6H); \(^{13}\)C NMR (101 MHz, DMSO-\( d_6 \)) \( \delta \) 180.32, 170.87, 133.32, 132.68, 131.69, 130.13, 127.82, 125.40, 99.50, 81.08, 24.57.

HRMS (ESI-MS, m/z): calculated m/z for \([C_{12}H_{11}BrO_3][-H]^+\): 280.9819, found: 280.9811.

4-hydroxy-5,5-dimethyl-3-(o-tolyl)furan-2(5H)-one (2t)

54.4 mg, 0.249 mmol, 62%, White powder; \( R_f \) (MeOH/DCM 1/10): 0.50;

\(^1\)H NMR (400 MHz, DMSO-\( d_6 \)) \( \delta \) 12.22 (s, 1H), 7.25 – 7.11 (m, 4H), 2.16 (s, 3H), 1.50 (s, 6H); \(^{13}\)C NMR (101 MHz, DMSO-\( d_6 \)) \( \delta \) 179.71, 171.51, 137.87, 131.25, 130.16, 129.73, 128.09, 125.79, 99.22, 80.75, 24.73, 19.94.

HRMS (ESI-MS, m/z): calculated m/z for \([C_{13}H_{14}O_3][+H]^+\): 219.1016, found: 219.1014.
4-hydroxy-5,5-dimethyl-3-(m-tolyl)furan-2(5H)-one (2v)

55.7 mg, 0.255 mmol, 64%; White powder; Rf (MeOH/DCM 1/10): 0.38;

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.55 (s, 1H), 7.74 – 7.66 (m, 2H), 7.23 (t, J = 7.7 Hz, 1H), 7.04 – 6.99 (m, 1H), 2.30 (s, 3H), 1.50 (s, 6H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 181.25, 171.54, 137.19, 131.36, 128.26, 127.62, 127.18, 124.27, 96.24, 79.99, 24.57, 21.73.

HRMS (ESI-MS, m/z): calculated m/z for [C$_{13}$H$_{14}$O$_3$] [M+H]$^+$: 219.1016, found: 219.1014.

4-hydroxy-5,5-dimethyl-3-(pyridin-2-yl)furan-2(5H)-one (2w)

61.2 mg, 0.298 mmol, 75%; White powder; Rf (MeOH/DCM 1/10): 0.78;

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.37 – 8.34 (m, 1H), 8.31 (d, J = 8.7 Hz, 1H), 8.18 – 8.12 (m, 1H), 7.29 – 7.24 (m, 1H), 1.34 (s, 6H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 197.64, 172.30, 149.90, 143.66, 138.33, 119.19, 117.88, 83.24, 82.63, 24.36.

HRMS (ESI-MS, m/z): calculated m/z for [C$_{11}$H$_{11}$NO$_3$] [M+H]$^+$: 206.0812, found: 206.0812.

4-hydroxy-5,5-dimethyl-3-(naphthalen-2-yl)furan-2(5H)-one (2x)
74.1 mg, 0.291 mmol, 73%; White powder; Rf (MeOH/DCM 1/10): 0.25;

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.44 (d, $J = 3.5$ Hz, 1H), 8.16 – 8.06 (m, 1H), 7.93 – 7.82 (m, 3H), 7.55 – 7.42 (m, 2H), 1.56 (s, 6H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$
181.81, 171.62, 133.31, 131.91, 129.19, 128.32, 127.86, 127.65, 126.48, 126.02, 125.54, 125.41, 96.22, 80.21, 24.61.

HRMS (ESI-MS, m/z): calculated m/z for [C$_{16}$H$_{14}$O$_3$] $[M-H]^{-}$: 253.0870, found: 253.0868.
References


$^1$H NMR, $^{19}$F NMR and $^{13}$C NMR spectra

4-(4-hydroxy-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-yl)benzonitrile (2a)
4-(4-hydroxy-5-methyl-2-oxo-5-phenyl-2,5-dihydrofuran-3-yl)benzonitrile (2b)
4-(5,5-diethyl-4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)benzonitrile (2c)
4-(4-hydroxy-5-methyl-2-oxo-5-phenyl-2,5-dihydrofuran-3-yl)benzonitrile  (2d)
4-(4-hydroxy-2-oxo-1-oxaspiro[4.6]undec-3-en-3-yl)benzonitrile (2e)
4-(4-hydroxy-2-oxo-1-oxaspiro[4.5]dec-3-en-3-yl)benzonitrile (2f)
4-(4-hydroxy-2-oxo-1-oxaspiro[4.6]undec-3-en-3-yl)benzonitrile (2g)
4-hydroxy-5,5-dimethyl-3-phenylfuran-2(5H)-one (2h)
3-(4-chlorophenyl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2j)
3-(4-bromophenyl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2k)
3-([1,1'-biphenyl]-4-yl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2l)
4-hydroxy-5,5-dimethyl-3-(p-tolyl)furan-2(5H)-one (2m)
ethyl 4-(4-hydroxy-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-yl)benzoate (2n)
4-hydroxy-5,5-dimethyl-3-(4-nitrophenyl)furan-2(5H)-one (2o)
4-hydroxy-5,5-dimethyl-3-(4-(trifluoromethyl)phenyl)furan-2(5H)-one (2p)
3-(4-benzoylphenyl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2q)
4-hydroxy-5,5-dimethyl-3-(4-(trifluoromethoxy)phenyl)furan-2(5H)-one (2r)
3-(2-bromophenyl)-4-hydroxy-5,5-dimethylfuran-2(5H)-one (2s)
4-hydroxy-5,5-dimethyl-3-(o-tolyl)furan-2(5H)-one (2t)
4-hydroxy-3-(3-methoxyphenyl)-5,5-dimethylfuran-2(5H)-one (2u)
4-hydroxy-5,5-dimethyl-3-(m-tolyl)furan-2(5H)-one (2v)
4-hydroxy-5,5-dimethyl-3-(pyridin-2-yl)furan-2(5H)-one (2w)
4-hydroxy-5,5-dimethyl-3-(naphthalen-2-yl)furan-2(5H)-one (2x)

[Chemical structure image]
4-hydroxy-5,5-dimethyl-3-phenylfuran-2(5H)-one-2\textsuperscript{13}C (2h')